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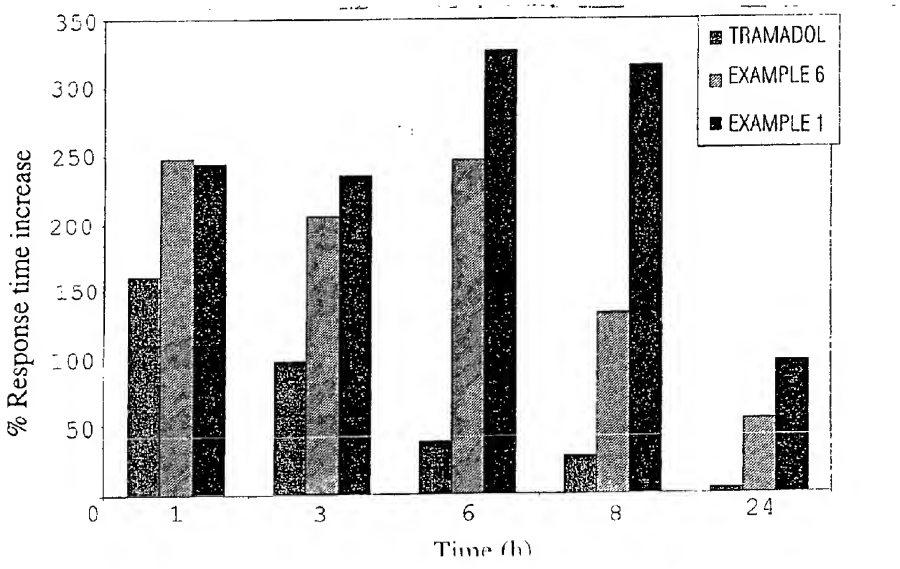
(54) NEW ESTERS DERIVED FROM SUBSTITUTED PHENYL-CYCLOHEXYL COMPOUNDS

(57) New csters derived from substituted phenyl cyclohexyl compounds, which are derived from Tramadol, process for obtaining them and their use for preparing a drug with analgesic properties. These new compounds of general formula (I) have a higher analges activcity, a lower toxicity and a longer effective time period than Tramadol.



EP 1 127 871 A1

Description

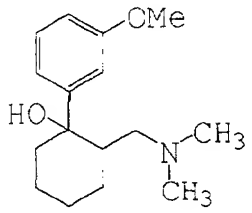
Field of the invention

[0001] The present invention relates to new esters derived from substituted phenyl-cyclohexyl compounds, which are derived from Tramadol. The obtained compounds have a higher analgesic activity, a lower toxicity and a longer effective time period than Tramadol.

Background of the invention

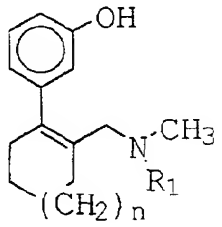
[0002] The treatment of pain is of great importance in the > field of medicine. The pharmacological agents presently used for the treatment of pain can be primarily classified into two large groups: opioid compounds and non-steroidal anti-inflammatories (NSAIs). The NSAIs are only useful in the case of light or moderate pain; severe pain has traditionally been treated with opiod compounds. However, these opioid compounds have several undesirable side effects, such as constipation, respiratory depression, tolerance and possibility of addiction.

[0003] US patent 3652589 describes a type of analgesic compounds with a structure of substituted cycloalkanol phenol ethers having a basic amino group in the cycloalkyl ring. Among them the (1R, 2R or 1S, 2S)-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol compound, generally known as Tramadol, is specially noted and specifically claimed in said patent.



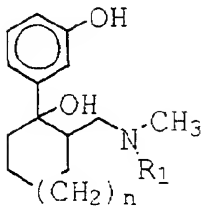
Tramadol

[0004] A series of products derived from the above, in which the dehydration in the cycloalkanol ring has occurred together with the demethylation of the methoxyl in the 3 position of the phenyl ring, of structure:



have been described in the Dutch patent NL 6610022.

[0005] This patent also describes products derived from those of said US patent, in which the methoxyl group in the 3 position of the phenyl ring has been demethylated. That is, products of structure:



[0006] O-demethyltramadol is included among those products described in this patent, said product having been described as one of the metabolization products of Tramadol (Von W. Lintz et al. *Arzneim-Forsch (Drug Res)* **31** (II); 1932-43 (1981). The analgesic activity of Tramadol is attributed to its (+) isomer (Lars Poulsen et al. *Clin. Pharmacol. Ther* (St. Louis) 1996, **60** (6), 636-644). However, there is no data as to the clinical use of the O-demethyltramadol metabolite.

[0007] More recently, in patent EP 753506, new derivatives of Tramadol have been described, which are O-demethylsubstituted, halogenated at position 1 and/or 3-cyclohexyl substituted.

[0008] Tramadol has an opioid agonist effect. However, the clinical experience with Tramadol shows that in spite of this, it does not present some of the side effects typical of the opioid agonists, such as respiratory depression (W. Vogel et al. *Arzneim. Forsch (Drug Res)* **28** (I), 183 (1978)), constipation (I. Arend et al. *Arzneim. Forsch (Drug Res)* **28** (I), 199 (1978), tolerance (L. Flohe et al., *Arzneim. Forsch (Drug Res)* **28** (I), 213 (1978)) and possibility of abuse (T. Yenagita et al., *Arzneim. Forsch (Drug Res)* **28** (I), 158 (1978)). Some side effects specific for Tramadol have been found, which are caused when it is injected intravenously (i.v.) and quickly, such as hot flushes and sweating.

[0009] Another of the disadvantages associated with Tramadol is its short effective time period (T. Matthiesen, T. Wohrmann, T.P. Coogan, H. Uragg, "*The experimental toxicology of tramadol: an overview", Toxicology Letters* **95,** 63-71, (1998)).

[0010] Based on the above background of the invention, the compounds with an analgesic activity similar to or higher than that of Tramadol and with a lower toxicity and with a higher effective time period are still of interest.

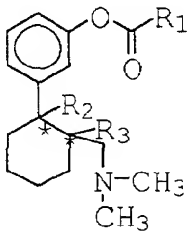
Description of the invention

[0011] The present invention relates to new esters of O-demethyltramadol or its 1,2-dehydrated derivative.

[0012] The analgesic activity of these compounds has been found to be higher than that of Tramadol with a lower toxicity and a longer effective time period when administered orally (see Figure 1).

[0013] In particular, the present invention describes and claims those products of general formula (I), its salts and optical isomers, as well as the process for obtaining them.

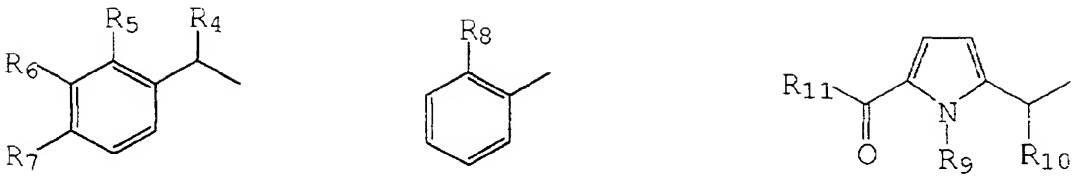
[0014] The products of the present invention are represented by the following general formula (I):



(I)

* Shows possibility of asymmetric carbons

where R_1 is:



A B or C

R_2 is: OH;
R_3 is: H;
or R_2 and R_3 together form a double bond;
R_4 is: H or C_1-C_3 alkyl;
R_5 is: H, NH_2, NH-R_{11} or O-R_{11};
R_6 is: H, CO-R_{11}, O-R_{11} or halogen;
R_7 is: H, C_1-C_5 alkyl, C_2-C_5 O-alkenyl, phenyl,
or R_6 and R_7 are -CH=CR_{12}-CR_{13}=CH-, forming an optionally substituted condensed aromatic ring;
R_8 is: OH, -O-CO-$N(CH_3)_2$ or NH-R_{11};
R_9 and R_{10} are: H or C_1-C_4 alkyl, whether equal or different,
or form a -CH_2- CH_2- bond;
R_{11} is: phenyl; phenyl optionally substituted by 1 or more of the following substituents: halogen (Cl, Br, I), NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, OH, or NH ;
R_{12} and R_{13} are: H, or C_1-C_6 O-alkyl, whether equal or different.

[0015] When R_1 is A, preferably, R_4 is methyl or H, R_5 is NH_2, 2,5-dichlorophenylamino or H, R_6 is substituted CO-phenyl or H, R_7 is isobutyl or H, or R_6 and R_7 form a substituted condensed aromatic ring.

[0016] More preferably, when R_1 is A, the products are:

- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(4-isobutyl-phenyl)-propionate
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate

[0017] When R_1 is B, preferably, R_8 is OH or -O-CO-$N(CH_3)_2$.

[0018] More preferably, when R_1 is B, the products are:

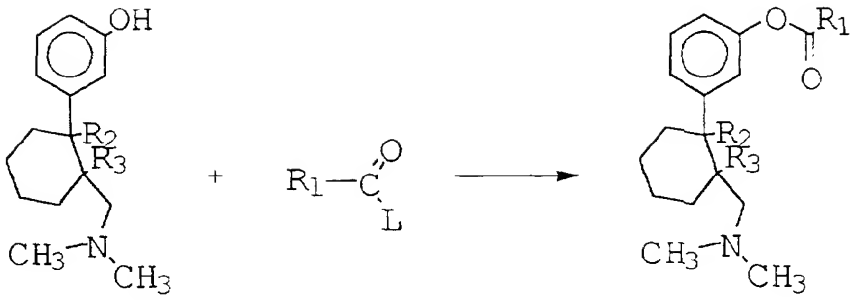
- 3- (2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-hydroxybenzoate
- 3-(2-dimethylaminomethyl-cyclohex-I-enyl)-phenyl 2-hydroxybenzoate
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-dimethylcarbamoyloxy-benzoate
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-dimethylcarbamoyloxy-benzoate.

[0019] When R_1 is C, preferably, R_9 is methyl or H or forms a -CH_2-CH_2- bond with R_{10}. More preferably, when R_1 is C, the products are:

- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 5-benzoyl-2,3-dihydro-IH-pyrrolizine-1-carboxylate

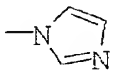
DESCRIPTION OF THE METHODS

[0020] The compounds of general formula (**I**) of the present invention can be obtained by a general process which is characterised by reacting a compound of general formula (**II**) with the corresponding acid or acid derivative of general formula **III**.



II III I

Where R_1, R_2, R_3 have the above defined meaning, and L = OH, halogen,



$O\text{-}R_{14}$ or - $CO\text{-}R_{15}$
being

R_{14} = $C_{1\text{-}6}$ alkyl, phenyl, optionally substituted phenyl, and
R_{15} = alkyl, a phenyl ring optionally substituted by one or more substituents or a heterocyclic ring optionally substituted by one or more substituents.

[0021] Preferably L is OH or halogen.

[0022] The reaction is carried out in an inert solvent, preferably dichloromethane, tetrahydrofuran, etc., in a temperature range of -20° to 120°C, preferably a range of 0° to 35°C, and preferably in the presence of a condensation promoting agent, such as carbonyldiimidazol, dicyclohexylcarbo-diimida, etc.

[0023] The compounds of formula (**II**) are obtained according to the methods disclosed in the literature (NL 6610022 or Flick *et al. Arzneim. Forsch/Drug Res.* (1978), **28** (I), 107-113).

Description of the pharmacological processes

Analgesic Activity Tests

[0024] The pharmacological activity of the products of the present invention was tested *in vivo* in several experimental models, which are known to evaluate the pain in animals.

a) Hot plate method

[0025] The method that was used is described by Eddy N.B. and Leimbach D. (J. Pharm. Exp. Ther. 107: 385-393, 1953). The analgesic effect of the products was evaluated analysing the behaviour of the animals on a hot surface at 55°C±1°C.

[0026] Male Swiss mice weighing 20-25 g were used. The compounds being tested were administered orally or intraperitoneally 1 hour o 30 minures before starting the test, respectively.

[0027] The process consisted of placing the animals on the plate and keeping them in a Plexiglas cylinder 25 cm high and 21 cm high. The time the animals took to jump off the hot surface was determined. The animals were selected before starting the test so that those that took longer than 10 seconds to jump off were not included in the group that would receive treatment.

[0028] 30 minutes after administering the product being tested, the test was repeated and the maximum time it took the animals to jump off was again recorded. Those animals that did not jump off after 60 seconds were removed from the plate to avoid any injuries and were recorded as 100 protection.

[0029] The results are expressed as the of jump time increase calculated as follows:

$$\%jump\ time\ increase = \frac{(treated\ jump\ time - base\ jump\ time)}{base\ jump\ tieme} \times 100$$

[0030] In order to determine the duration of the analgesic effect of the orally administered products, the analgesic activity was evaluated on the hot plate 1, 3, 6, 8, and 24 hours after the administration of the product, as well as the control group which received treatment only with the vehicle. The base responses were evaluated at 30 and 5 minutes prior to administering the products.

b) Determination of the DL50 in the products.

[0031] (EUDRA/S/87/011, *Single Dose Toxicity*, European Directive 75/318/EEC) (ICH S4, Toxicity Studies, single dose and repeated dose, CPMP vol III Feb. 57, *Single dose toxicity*)

[0032] Male Swiss mice of the same batch weighing 20-25 g are used in order to estimate the acute toxicity of the products.

[0033] Prior to administering the products, the animals were forced to fast for 12 hours with no intake of food but free access to water. Several subgroups of 10 animals were randomly selected and orally given increasing doses of the products in single administration, after which they remained under observation for a period of 14 days with free access to water and food. Finally, the number of dead animals of each subgroup was quantified and the value of the DL50 was calculated (1-2).

Description of the figure

[0034] Figure 1 shows the analgesic effect on the hot plate test with mice in terms of time, expressed as percentage of increased response time with relation to the time (in hours) elapsed since the administration of the product. It is represented in grey for Tramadol, striped for compound (I) of example 6 and in black for example 1.

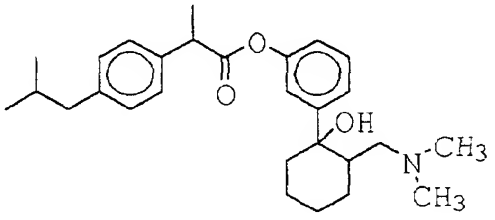
EXPERIMENTAL PART

1.1. Synthesis examples

EXAMPLE 1

Synthesis of 3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenyl 2-(4-isobutyl-phenyl)-propionate

[0035]



[0036] 0.76 g (4.8 mmol) of carbonyldiimidazol were added to 1 g (4.8 mmol) of (±)-Ibuprofen in 60 ml of dry THF. The reaction was kept at room temperature for 2 h, after which a 60% solution of 0.59 g (2.4 mmol) of (RR,SS)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenol previously treated with 0.1 g (2.5 mmol) of sodium hydride in mineral oil was added.

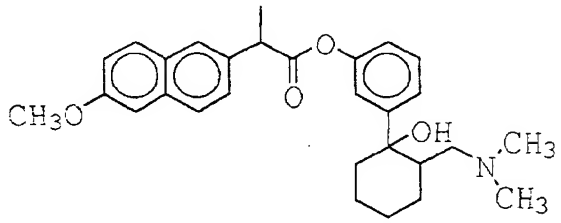
[0037] The reaction was left at room temperature for 16 h. It was concentrated to dryness and the residue was treated with 100 ml of dichloromethane and washed with 2 x 50 ml of NaOH 1N and then with 100 ml of H_2O.

[0038] The organic phase was dried and concentrated and the residue was chromatographed on silica gel. By eluting with CH_2Cl_2/EtOH 98/2 to 96/4, 0.65 g (62%) of pure product was obtained as a colourless oil.
^{1}H-NMR ($CDCl_3$): 0.90 (d, 6H); 1.20-2.20 [m, 21H including 1.6 (d, 3H) and 2.05 (s, 6H)]; 2.32-2.44 (d.d, 1H); 2.47 (d, 2H); 3.92 (c, 1H) ; 6.78-6.86 (m, 1H); 7.12 (d, 2H) ; 7.18 (s.a., 1H) ; 7.22-7.34 (m, 4H).

EXAMPLE 2

Synthesis of 3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate

[0039]

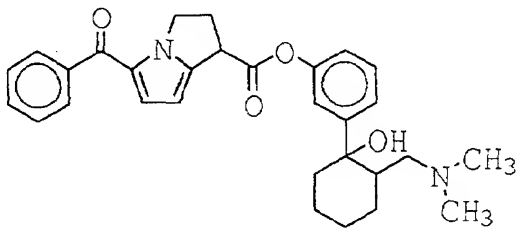


[0040] Following the process described in example 1 and substituting the (±)-Ibuprofen with (+)-6-methoxy-α-methyl-2-naphthylacetic acid (Naproxen) the title product is obtained as an oil with a 40% yield.
^{1}H-NMR ($CDCl_3$) : 1.20-2.20 [m, 20 H includina 1.67 (d, 3H,) and 2.06 (s, 6H]; 2.35 (dd, 1H); 3.91 (s, 3H); 4.09 (c, 1H) ; 6.75-6.85 (m, 1H); 7.00 (s.a., 1H); 7.15-7.35 (m, 4H); 7.50 (d.d, 1H); 7.70-7.80 (m, 3H).

EXAMPLE 3

Synthesis of 3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenyl 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate

[0041]

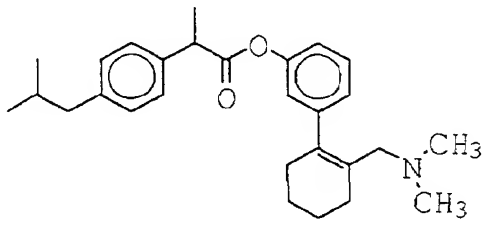


[0042] Following the process described in example 1 and substituting the (±)-Ibuprofen with (±) ketorolac (5-benzoyl-1,2-dihydro-lH-pyrrolizine-l-carboxylic acid) the title product is obtained as an oil.
^{1}H-NMR ($CDCl_3$): 1.20-2.20 (m, 17H); 2.40 (d.d, 1H); 2.80-3.10 (m, 2H); 4.28-4.72 (m, 3H); 6.26 (d, 1H); 6.87 (d, 1H); 6.90-6.98 (m, 1H); 7.30-7.60 (m, 6H); 7.78-7.88 (m, 2H)

EXAMPLE 4

Synthesis of 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate

[0043]



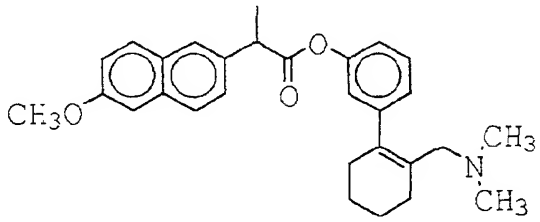
[0044] Following the process described in example 1 and substituting the (RR,SS)-3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenol with 3-(2-dimethylaminomethyl-1-cyclohex-I-enyl)-phenol the title product is obtained as an oil.

^{1}H-NMR ($CDCl_3$) : 0.90 (d, 6H); 1.60 (d, 3H); 1.62-1.98 (m, 4H); 2.02 (s, 6H); 2.10-2.25 (m, 4H); 2.45 (d, 2H); 2.70 (s. a., 2H); 3.92 (c, 1H); 6.70 (d, 1H); 6.82-6.90 (m, 2H); 7.12 (d, 2H); 7.20-7.32 (m, 3H).

EXAMPLE 5

Synthesis of 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2- (6-methoxy-naphthalen-2-yl)-propionate

[0045]



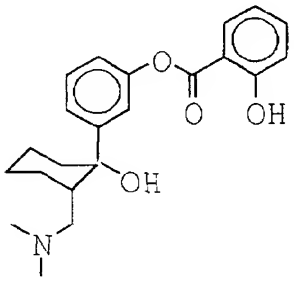
[0046] Following the process described in example 1 and substituting the (±)-Ibuprofen with (+)-6-methoxy-α-methyl-2-naphthalenacetic acid (Naproxen) and the (RR,SS)-3-(2-dimethylaminomethyl-I-hydroxy-cyclohexyl)-phenol with 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenol the title product is obtained as an oil.

^{1}H-NMR ($CDCl_3$): 1.60-1.76 (m, 4H); 1.68 (d, 3H); 2.02 (s, 6H); 2.10-2.24 (m, 4H); 2.66 (s, 2H); 3.92 (s, 3H); 4.09 (c, 1H); 6.70 (d, 1H); 2.82-2.92 (m, 2H); 7.12-7.28 (m, 3H); 7.50 (dd, 1H); 7.70-7.78 (m, 3H).

EXAMPLE 6

3- (2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl (RR-SS)-2-hydcoxybenzoate

[0047]

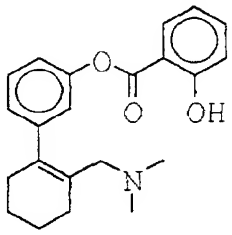


[0048] To a solution of 7.3 g (29.3 mmol) of (RR-SS)-3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenol and 2.6 g (32.5 mmol) of pyridine in 50 ml of CH Cl a 5.8 g (29.3 mmol) solution of acetylsalicyloyl chloride in 50 ml of CH_2Cl_2 was added dropwise at 0°C. The mixture was kept at 0°C for 10 h, 100 ml of methanol and 100 ml of HCl 1N were added and it was kept at 25°C for 4 days. After evaporating the methanol and basifying to pH 8.5 with Na_2CO_3, it was extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by silica gel chromatography, by eluting with CH_2Cl_2/MeOH/NH_4OH 1000:30:3, to obtain 1.7 g (16%) of the title compound as a yellow oil.
^{1}H-NMR ($CDCl_3$): 1.20-2.25 (m, 16H) including 2.11 (s, 6H); 2.45 (dd, 1H); 6.90-7.15 (m, 3H); 7.30-7.48 (m, 3H); 7.48-7.62 (m, 1H); 8.08 (dd, 1H); 10.55 (s, 1H, exchange with D_2O)

EXAMPLE 7

3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-hydroxybenzoate

[0049]

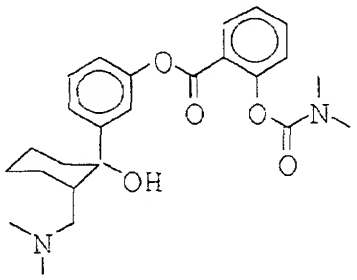


[0050] Starting from 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenol and following the process described in example 6, the title compound was obtained as a yellow oil.
^{1}H-NMR ($CDCl_2$): 1.60-1.80 (m, 4H); 2.10 (s, 6H) ; 2.15-2.35 (m, 4H); 2.75 (s, 2H); 6.90-7.10 (m, 5H); 7.40 (t, 1H); 7.55 (t, 1H); 8.10 (d, 1H); 10.50 (sa, 1H, exchange with D_2O).

EXAMPLE 8

3- (2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl (RR-SS)-2-dimethylcarbamoyloxy-benzoate

[0051]

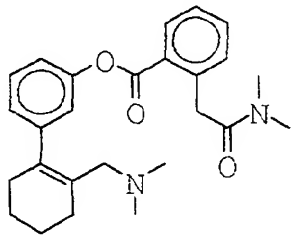


[0052] A solution of 1.82 g (8.0 nmol) of 2-dimethylcarbamoyloxybenzoyl chloride in 25 ml of CH_2Cl_2 was added dropwise at 0°C to a solution of 1.9 g (7.7 nmol) of (RR-SS)-3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenol and 0.73 g (9.2 nmol) of pyridine in 50 ml of CH_2Cl_2. The mixture was maintained at 0° for 10 h, and poured over frozen water, the phases were separated and the aqueous phase was extracted with 100 ml of CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel by eluting with CH_2Cl_2/acetone 80:20. 570 mg (48%) of the title compound was obtained as an orange oil.
^{1}H-NMR ($CDCl_3$): 1.30-1.90 (m, 9H) ; 2.05 (m, 1H); 2.10 (s, 6H); 2.45 (dd, 1H); 2.95 (s, 3H); 3.05 (s, 3H); 7.00-7.10 (m, 1H); 7.20 (d, 1H); 7.30-7.40 (m, 4H); 7.60 (t, 1H) ; 8.15 (d, 1H).

EXAMPLE 9

3- (2-dimethylaminomethyl-cyclohex-1-enyl) -phenyl 2-dimethylcarbamoyloxy-benzoate

[0053]



[0054] Starting from 925 mg (4.0 mmol) of 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenol and following the process described in example 8, 190 mg (32%) of the title compound was obtained as a yellow oil.
^{1}H-NMR ($CDCl_3$): 1.70 (m, 4H) ; 2.07 (s, 6H); 2.10-2.30 (m, 4H); 2.75 (s, 2H); 2.95 (s, 3H); 3.10 (s, 2H); 6.90 (s, 1H); 6.95 (d, 1H); 7.05 (d, 1H); 7.20 (d, 1H) ; 7.30-7.45 (m, 2H); 7.65 (t, 1H) ; 8.20 (d, 1H).

Examples of pharmacological results

[0055] Table 1 below shows the results of the pharmacological activity of several examples of the invention product, as well as Tramadol. The results are expressed as percentage of increased response time on the hot plate test.
[0056] Table 2 shows the acute toxicity figures of Tramadol and of examples of the invention product, where the lower toxicity of the latter can be observed.

Analgesic activity in mice of the products on the hot plate

[0057]

TABLE 1

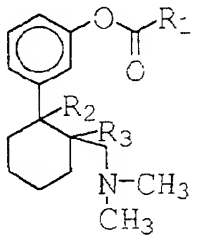
PRODUCT (15 mg/kg, intraperitoneal adm.)	% response time increase (n = 20)
Tramadol	218±98
EXAMPLE 1	568±100
EXAMPLE 2	539±50
EXAMPLE 3	416±146
EXAMPLE 4	333±134
EXAMPLE 5	356±151
EXAMPLE 6	546±63
EXAMPLE 7	634±42
EXAMPLE 8	327±65
EXAMPLE 9	405±13

TABLE 2

PRODUCT (20 µmol/kg, oral adm.)	**% response time increase on hot plate** (n= 20-40)	**DL50 approx. (mg/kg) Oral adm. Oral adm.**
TRAMADOL	87±23	350
EXAMPLE 6	248±72	550
EXAMPLE 1	210±88	900

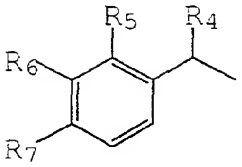
Claims

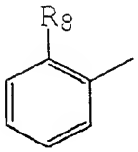
1. Compound of general formula (I) :

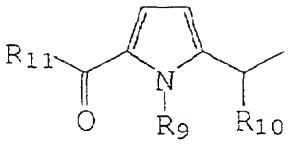


(I)

where R is:







A B or C

R_2 is: OH;
R_3 is: H
or R_2 and R_3 together form a double bond;
R_4 is: H or C_1-C_3 alkyl;
R_5 is: H, NH_2 , NH-R_{11} or O-R_{11};
R_6 is: H, CO-R_{11}, O-R_{11} or halogen;
R_7 is: H, C_1-C_5 alkyl, C_2-C_5 O-alkenyl, phenyl,
or R_6 and R_7 are -CH=CR_{12}-CR_{13}=CH-, forming an optionally substituted condensed aromatic ring;
R_8 is: OH, -O-CO-$N(CH_3)_2$ or NH-R_{11} ;
R_9 and R_{10} are: H or C_1-C_4 alkyl, whether equal or different,
or form a -CH_2- CH_2- bond;
R_{11} is: phenyl; phenyl optionally substituted by 1 or more of the following substituents: halogen (Cl, Br, I), NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, OH, or NH_2;
R_{12} and R_{13} are: H, or C_1-C_3 O-alkyl, whether equal or different; its salts and optical isomers.

2. Compound as claimed in claim 1, **characterised in that** R_1 is A, and R_4 is methyl or H, R_5 is NH_2, 2,5-dichlorophenylamino, or H, R_6 is substituted CO-phenyl or H, R_7 is isobutyl or H, or R_6 and R_7 form a substituted condensed aromatic ring.

3. Compound as claimed in claim 1, **characterised in that** R_1 is B, and R_8 is OH or -O-CO-$N(CH_3)_2$.

4. Compound as claimed in claim 1, **characterised in that** R_1 is C, and R_9 is methyl or H, or forms a -CH_2-CH_2- bond with R_{10}, and R_{11} is phenyl or tolyl.

5. Compound as claimed in claim 2, **characterised in that** it is selected from one of the following:

- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(4-isobutyl-phenyl)-propionate;
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate;

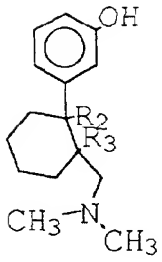
6. Compound as claimed in claim 3, **characterised in that** it is selected from one of the following:

- 3-(2-dimethylaminomethyl-I-hydroxy-cyclohexyl)-phenyl 2-hydroxybenzoate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-hydroxybenzoate;
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-dimethylcarbamoyloxy-benzoate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-dimethylcarbamoyloxy-benzoate.

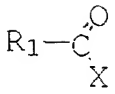
7. Compound as claimed in claim 4, **characterised in that** it is selected from one of the following:

- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate.

8. Process for obtaining a compound as claimed in claim 1, **characterised in that** a compound of formula (**II**) is reacted with a compound of formula (**III**):



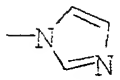
II



III

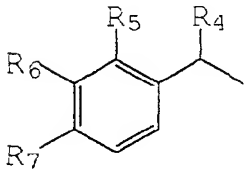
where:

R_2 = OH
R_3 = H
or R_2 and R_3 together form a double bond;
X = OH, halogen,

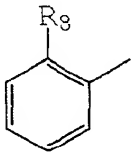


,

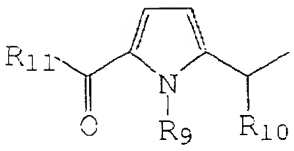
O-R_{14} or - CO-
R_{14} = C_{1-6} alkyl, phenyl, optionally substituted phenyl, and
R_{15} = alkyl, a phenyl ring optionally substituted by one or more substituents or a heterocyclic ring optionally substituted by one or more substituents;
R_1:



A



B



C

R_4 is: H or C_1-C_3 alkyl;
R_5 is: H, NH_2, NH-R_{11} or O-R_{11} ;
R_6 is: H, CO-R_{11}, O-R_{11} or halogen;
R_7 is: H, C_1-C_5 alkyl, C_2-C_5 O-alkenyl, phenyl,
or R_6 and R_7 are -CH=CR_{12}-CR_{13}=CH-, forming an optionally substituted condensed aromatic ring;
R_8 is: OH, -O-CO-N$(CH_3)_2$ or NH-R_{11} ;
R_9 and R_{10} are: H or C_1-C_4 alkyl, whether equal or different,
or form a -CH_2- CH_2- bond;
R_{11} is: phenyl; phenyl optionally substituted by 1 or more of the following substituents: halogen (Cl, Br, I), NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, OH, or NH_2;
R_{12} and R_{13} are: H, or C_1-C_3 O-alkyl, whether equal or different;

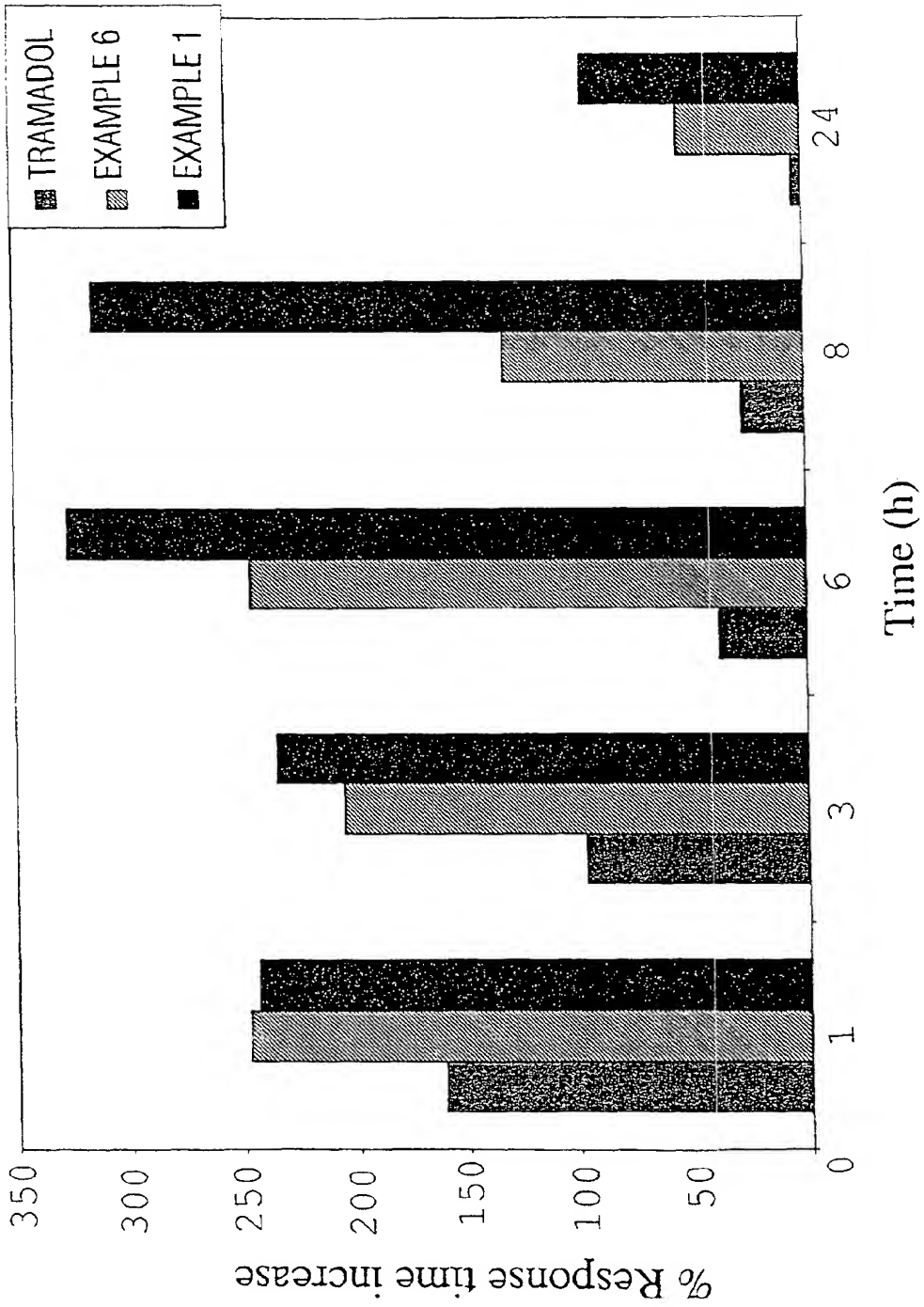
in an inert solvent, in a temperature range of -20° to 120°C, in the presence or absence of a condensation promoting agent.

9. Process as claimed in claim 8, **characterised in that** said inert solvent is dichloromethane or tetrahydrofuran.

10. Process as claimed in claim 8, **characterised in that** said condensation promoting agent is carbonyldiimidazol or dicyclohexylcarbo-diimida.

11. Process as claimed in claim 8, **characterised in that** said temperature range is from 0° to 35°C.

12. Use of a compound of general formula (I) as claimed in any of claims 1 to 7 for preparing a drug for the treatment of pain.


TRAMADOL
EXAMPLE 6
EXAMPLE 1
% Response time increase
350
300
250
200
150
100
50
0
1
3
6
8
24
Time (h)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/00352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C219/26 C07D207/337 A61K31/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	GB 997 399 A (CHEMIE GRUNENTHAL GMBH) 7 July 1965 (1965-07-07) claims 2,7,8,15	1-12
A	US 3 652 589 A (FLICK KURT ET AL) 28 March 1972 (1972-03-28) claims 2-23	1-12
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2000	21 03. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Elena Albarran

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INTERNATIONAL SEARCH REPORT

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